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Effect of Chronic Cocaine on Reproduction in Female House Mice

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CHEN, C.-J. AND J. G. VANDENBERGH. *Effect of chronic cocaine on reproduction in female house mice.* PHARMACOL BIOCHEM BEHAV 48(4) 909-913, 1994.—The effect of chronic cocaine exposure on the reproductive success of juvenile female house mice was studied. We followed two generations of female mice to examine the consequence of cocaine treatment on developmental and reproductive parameters such as weight gain, first estrus, impregnation, fertility, and maternal success. Twenty-two-day-old female mice were given cocaine at a daily total of 40 mg/kg body weight, delivered by two SC injections of 20 mg/kg each, until they were mated and inseminated by experienced males. The treatment attenuated weight gain and delayed puberty in the females but had no discernible effect on their pups. Administration of cocaine to lactating mothers decreased the weaning weight of their pups. Juvenile females previously nursed by mothers receiving cocaine and receiving 40 mg/kg cocaine daily themselves were impregnated at older ages than controls. Nevertheless, once these juveniles reached puberty, they mated successfully and their reproductive parameters did not differ from those of control mice. Thus, chronic cocaine treatment of juvenile female mice slows body growth and development but has little effect on the offspring produced later when they reached adulthood.

Cocaine Reproduction Juveniles Female Mice

IN MAMMALS, a complex series of physiological and behavioral events must be orchestrated to ensure reproduction. The reproductive success of a female animal may be modulated through: a) delay or acceleration of puberty; b) alteration of estrous cyclicity; c) number of ova released; d) male preference; e) number of embryos implanted; f) number of viable fetuses born; g) number of healthy pups surviving to weaning; and h) reproductive performance of her pups.

Cocaine is likely to affect various aspects of female reproduction by altering brain dopaminergic and adrenergic systems, because it can modulate brain monoamine neurons by blocking reuptake of catecholamines and serotonin. Neuroendocrine studies have revealed that cocaine affects the hypothalamic-pituitary release of gonadotropins and prolactin (7,9-11). One early study on female ovariectomized rats shows that cocaine at 10 to 20 mg/kg body weight increased and at 40 mg/kg decreased concentration of serum luteinizing hormone. The concentration of follicle-stimulating hormone was not affected, but prolactin levels were decreased by cocaine at either dose (13). In adult female rats, cocaine disrupts estrous cyclicity and normal rate of ovulation (7). It was also found to suppress mating-induced ovulation in the rabbit (5).

The effect of prenatal exposure to cocaine has been examined in many studies in recent years. It is well recognized that cocaine exposure during pregnancy can produce devastating effects on fetuses (12). However, comprehensive studies do not exist to determine whether chronic cocaine exposure during the juvenile stage can have a significant effect on life history traits important to the reproductive success of a female. The reported cocaine inhibition of GnRH may have a more serious impact during the juvenile stage than in adulthood. On the other hand, studies report a lack of neurochemical evidence for neurotoxic effects of repeated cocaine administration in the rat brain (8,16).

Recently, we showed that a 7-day prepubertal cocaine treatment at 30 or 40 mg/kg/day but not at 10 or 20 mg/kg/day attenuated the response of juvenile female mice toward the puberty acceleration pheromone contained in male mouse urine (2). We are interested in learning whether chronic cocaine exposure delays puberty in juvenile female mice and, if it does, whether this delay costs the reproductive success of these animals. In the present study, we examined several developmental and reproductive traits in two generations of female mice to begin to clarify the effect of chronic cocaine exposure on reproduction.

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METHOD

Swiss Webster albino mice produced in our breeding colony were used. They were maintained on a 14 L : 10 D cycle with lights on at 0600, and were provided with food and water ad lib. Juvenile females were weaned at 21 days of age (D21) and randomly assigned to treatments: subcutaneous (SC) saline injections at 10 ml/kg body weight and cocaine injections at daily doses of 20 or 40 mg/kg body weight. Each weanling was housed individually in a (11-1/2 × 7-1/2 × 5) cage and kept in a room containing female mice only. Mating was carried out by transporting females to another room containing singly caged adult male mice and placing one female in a male's cage.

Experiment 1: Effect of Repeated, High Dose Cocaine Exposure on the Development and Reproductive Performance of Juvenile Female Mice

Female weanlings from our breeding colony were randomly divided into two groups of 13 and 15 mice each. Starting from the morning of D22, animals in the control group were given two injections of saline each day while those in the experimental group were given two injections of cocaine hydrochloride at 20 mg/kg body weight each (Sigma Chemical Co., St. Louis, MO; prepared with 0.9% saline). The morning injection was given between 0900 and 1000 h and the afternoon injection was given between 1600 and 1700 h. While being prepared for morning injection, each animal was weighed and inspected for vaginal opening. Animals with open vaginas were smeared daily to time the onset of epithelial cell cornification signaling the first estrus (4). (Vaginal opening in the mouse is not a good measure of puberty as it is in the rat.)

Female mice were first introduced to experienced male mice after their afternoon injections on D35. On the following morning, all females were removed and inspected for vaginal plugs. To avoid the complication of fetal cocaine exposure, animals showing plugs were no longer treated, although those showing no sign of insemination were injected again for the day and mated with a different male in the evening. Females of both groups were allowed a maximum of 7 nights to get impregnated. The following measures were taken:

1. The number of animals in each group that were inseminated and the number that became pregnant.
2. For animals who completed their pregnancy—gestation period, litter size, the sex ratio, and birth weight of pups.
3. At 1 week after birth—pup death, pup weights, the number of mothers who lost pups during the week.

Experiment 2: Effect of Extended Cocaine Treatment on the Reproductive Performance of Juvenile Female Mice

We extended the course of cocaine treatment into the nursing period of pups. All litters from Experiment 1 were culled to 10 pups on postpartum day 7 and reared by their own mothers until 21 days of age. Mothers who had less than 10 surviving pups were given same age pups from other females of the same group to make a total of 10. Starting on postpartum day 7, disregarding the treatment they received during the juvenile stage, all lactating mothers were treated with cocaine at a daily dose of 40 mg/kg body weight (administered through two SC injections) until their pups were weaned.

Starting at D22, weanlings began to receive treatments of their own. Fifteen female weanlings from mothers who received saline as juveniles (SA) were given one cocaine injection of 20 mg/kg body weight in the morning and one saline injection in the afternoon (group SA-cc20; cc stands for animals received cocaine indirectly from nursing mother; 20 stands for the daily total of cocaine received after weaning). Forty-eight female weanlings from mothers who received cocaine as juveniles (CC) were divided into three groups of 16 each. One of these groups was treated daily with two injections of saline (group CC-cc00). The second group was treated with one injection of cocaine and one injection of saline (group CC-cc20) and the third group two injections of cocaine (group CC-cc40).

Because all mothers from Experiment 1 were designated to receive cocaine treatment for the second and third postpartum weeks, five nursing mothers were randomly picked from our breeding colony to provide 15 female weanlings for the main control group of this experiment (group NO-sa00, cocaine free). These mothers received no treatment as juveniles, but were treated daily with two injections of saline during the second and third postpartum weeks. Once weaned, juvenile females of the control group began to receive two saline injections daily. They and members of treatment groups were introduced to experienced males at the age of 33 days. All females were allowed a maximum of 9 nights to get impregnated and treatments were stopped at the first sign of insemination. Measures taken in Experiment 1 were taken again from these animals.

Data Analysis

Fisher's exact test was used to evaluate the number of animals in each treatment group who displayed a vaginal plug, became pregnant, or lost pups during the first postpartum week. *t*-Test and analysis of variance were used to assess group differences of other growth, developmental, and reproductive parameters. Post hoc tests of significant effects were performed by using Dunnett's procedure to compare multiple treatment groups with the main control and using Duncan's new multiple-range test for comparisons among treatment groups. Differences were considered significant at the 5% level ($p < 0.05$).

RESULTS

Experiment 1

Repeated cocaine administration to juvenile female house mice at 40 mg/kg body weight/day decreased weight gain (Ta-

TABLE 1

BODY WEIGHT CHANGE OF JUVENILE FEMALE MICE TREATED WITH COCAINE AT 40 mg/kg/DAY BETWEEN AGES OF 22 DAYS AND 35 DAYS, COMPARED TO CONTROLS TREATED WITH SALINE

Treatment	Saline	Cocaine
Sample size	13	15
Body weight (g)		
D22	16.6 ± 0.2	17.2 ± 0.3
D28	21.7 ± 0.4	19.9 ± 0.5*
D35 first mating	24.6 ± 0.5	23.8 ± 0.6
Percent weight increase		
D22–D28	30.7 ± 1.5	16.2 ± 2.6*
D28–D35	13.4 ± 1.0	19.5 ± 2.6*
D22–D35	48.1 ± 2.5	38.5 ± 3.5*

Values listed are either counts or means ± SEM.
*Significantly different from saline controls, $p < 0.05$.

ble 1) and delayed first estrus for almost 3 days (Table 2). The inhibition on body growth was strongest during the first week. Cocaine did not affect the age at which animals were impregnated, the number of animals impregnated, or the duration of gestation.

Young females who had received cocaine as juveniles gave birth to fewer pups, but the sex ratio and mean pup weight of their litters were similar to those of saline treated mothers (Table 2). Pup death occurred in both groups during the first postnatal week. Four out of 12 saline treated mothers and 3 out of 14 cocaine treated mothers lost pups. The surviving pups from both groups gained about the same amount of weight during the first postnatal week. No pup death occurred after the first week, although all nursing mothers were receiving cocaine at 40 mg/kg/day between postpartum days 7 and 21.

Experiment 2

The female offspring of saline-treated mothers (group SA—cc20). The pups started to receive cocaine from their mothers' milk (15) at postnatal day 7. After weaning, juvenile females were treated with cocaine at 20 mg/kg/day. Their D22 weight and D33 weight were both significantly lower than those of mice in the control group (Table 3). However, they gained about the same amount of weight between D22 and D33 as controls (SA-cc20 : 8.8 g vs. NO-sa00 : 8.7 g). The extended low-dose cocaine treatment did not delay the age of impregnation, but decreased the duration of gestation (Table 4). When their litters were compared with those of controls, no difference in litter size, sex ratio, pup weight, and pup growth was found. No mother in the 20 mg/kg cocaine-treated group lost pups, although four controls lost pups during the first postpartum week.

TABLE 2

THE DEVELOPMENTAL AND REPRODUCTIVE OUTCOME OF JUVENILE FEMALE MICE TREATED WITH EITHER SALINE OR COCAINE AT 40 mg/kg/day BETWEEN POSTNATAL DAY 22 AND THE DAY OF INSEMINATION BY MALE MICE

Treatment	Saline	Cocaine
Age in days for		
Vaginal opening	25.1 ± 0.4	24.3 ± 0.3
First estrous	29.3 ± 0.5	32.4 ± 1.2*
Showing plug	37.9 ± 0.3	37.9 ± 0.3
Number (%) of animals		
Plugged	13 (100%)	15 (100%)
Pregnant	12 (92.2%)	14 (93.3%)
Lost pups in week 1	4 (33.3%)	3 (21.4%)
Gestation (days)	18.7 ± 0.1	18.8 ± 0.1
Male ratio	0.51 ± 0.05	0.51 ± 0.06
Litter size		
Day 1	13.3 ± 0.5	11.5 ± 0.5*
Day 7	12.9 ± 0.4	11.1 ± 0.5*
Averaged pup weight (g)		
Day 1	1.56 ± 0.03	1.57 ± 0.02
Day 7	4.25 ± 0.12	4.47 ± 0.14
Day 18	8.64 ± 0.25	8.56 ± 0.31

Values listed are either counts or means ± SEM.
*Significantly different from saline controls, $p < 0.05$.

The female offspring of cocaine-treated mothers (groups CC-cc00, CC-cc20, CC-cc40). The pups were nursed by mothers who received cocaine at 40 mg/kg/day as juveniles and received cocaine again during the second and third weeks of nursing. After weaning, juvenile females were treated daily with either saline or cocaine at 20 or 40 mg/kg. Their weaning weights were lower than that of controls (Table 3). Cocaine treatment during the period between D22 and D33 attenuated weight gain in a dose-dependent manner. Juveniles treated with saline gained more weight than controls, but those treated with 40 mg/kg cocaine gained much less weight (NO-sa00 : 8.6 g; CC-cc00 : 9.2 g; CC-cc20 : 8.5 g; CC-cc40 : 5.3 g).

Female mice treated with cocaine at 40 mg/kg/day were impregnated at older ages than their siblings in the other two groups and animals in the control group (Table 4). The number of animals impregnated within the 9-night mating period was low, although the difference was not statistically significant. Nevertheless, cocaine exposure, low dose or high dose, caused no adverse effect on the outcome of pregnancy. There was no difference in litter size, sex ratio, pup weight, or pup growth. One female out of the CC-cc20 group lost pups during the first postpartum week, but four out of the CC-cc00 group and three out of the CC-cc40 group lost pups.

Effects of mother's prepubertal cocaine exposure on their cocaine-treated offspring (SA-cc20 vs. CC-cc20). Juvenile females in groups SA-cc20 and CC-cc20 received the same kind of cocaine treatment after birth—low-dose cocaine from postnatal day 7 to the day of insemination, but their mothers were treated differently as juveniles. These two groups of animals showed close similarity in all growth, developmental, and reproductive parameters examined (Tables 3 and 4).

DISCUSSION

This study was designed to examine the effect of chronic cocaine exposure on the reproductive success of juvenile female mice. Our results show that the main adverse effect of cocaine on female mice is the inhibition of growth and development. Pups nursed by mothers receiving cocaine failed to reach the weaning weight of controls. Repeated cocaine exposure after weaning further attenuated the weight gain of juveniles. The effect of cocaine on body growth was dose dependent and most significant during the first week of treatment. In addition to its effect on growth, prepubertal cocaine treatment at 40 mg/kg/day delayed puberty. In juvenile females who had been exposed to cocaine while nursing, this treatment further postponed their impregnation by experienced males.

Although the decreased weight gain in cocaine-treated juvenile female mice could be the result of decreased food and water consumption (1,7), the low weaning weight of pups nursed by mothers receiving cocaine might have been resulted from impaired maternal care as well as inadequate nursing. Cocaine can present an adverse effect on the maternal behavior by modulating monoamines involved in both hormonal and nonhormonal factors responsible for maternal behavior (6). It was reported to impair the parenting ability of both male and female rats, with and without previous parenting experience (17). Meanwhile, administration of radioactive cocaine to lactating rat dams brought about the milk/blood cocaine ratio of 7.8 (15). Thus, cocaine administered to lactating mothers becomes readily available to their suckling pups.

Among female pups nursed by cocaine-receiving mothers, postweaning cocaine treatment at 20 mg/kg/day brought about as much weight gain between D22 and D33 as that of the control group. Meanwhile, saline treatment resulted in

TABLE 3

BODY WEIGHT CHANGE OF JUVENILE FEMALE MICE NURSED BY MOTHERS RECEIVING EITHER SALINE OR COCAINE WHILE LACTATING AND RECEIVED SALINE OR COCAINE AT 20 OR 40 mg/kg/day THEMSELVES AFTER WEANING

Group	NO-sa00	SA-cc20	CC-cc00	CC-cc20	CC-cc40
Dame treatment					
Before mating	None	Saline	Cocaine (40)	Cocaine (40)	Cocaine (40)
While nursing	Saline	Cocaine (40)	Cocaine (40)	Cocaine (40)	Cocaine (40)
Treatment	Saline	Cocaine (20)	Saline	Cocaine (20)	Cocaine (40)
Sample size	15	15	16	16	16
Body weight (g)					
D22	14.8 ± 0.2	12.1 ± 0.3*	11.6 ± 0.3*	12.5 ± 0.4*	12.0 ± 0.4*
D28	20.9 ± 0.3	17.3 ± 0.6*	17.3 ± 0.5*	17.8 ± 0.5*	15.0 ± 0.5*†‡
D33 first mating	23.4 ± 0.2	20.8 ± 0.6*	20.9 ± 0.5*	21.0 ± 0.5*	17.3 ± 0.5*†‡
Percent weight increase					
D22–D28	41.7 ± 1.5	42.8 ± 2.3	49.0 ± 2.9*	42.5 ± 1.7†	24.6 ± 1.6*†‡
D28–D33	12.0 ± 0.7	21.2 ± 1.1*	20.8 ± 1.4*	18.6 ± 1.6*	15.9 ± 2.0†
D22–D33	58.7 ± 1.7	72.9 ± 2.6*	80.2 ± 4.6*	69.1 ± 3.5†	44.2 ± 2.5*†‡

Values listed are either counts or means ± SEM.
*Significantly different from NO-sa00 controls, $p < 0.05$.
†Significantly different from CC-cc00, ‡significantly different from CC-cc20; $p < 0.05$. Comparisons are made among the offspring of CC mothers only.

more weight gain than that of the control group. This seems to indicate that, once cocaine exposure is stopped at weaning, juvenile mice are able to compensate partially for the attenuated weight gain during nursing.

Repeated 40 mg/kg/day cocaine exposure delayed the first estrus in juvenile female mice but did not prevent them from getting impregnated within the designated period. In females that had been exposed to cocaine as pups, the cocaine-induced puberty delay became reproductively significant, because some of them were not ready to mate when they were introduced to experienced males. On the other hand, cocaine at the low daily dose of 20 mg/kg caused no discernible developmental or reproductive effect. Thus, the developmental and reproductive fate of female weanlings of cocaine-taking mothers is mostly determined by their later direct exposure to the drug.

Although our data show significant growth and development effects of cocaine on pups and juvenile females, it is also clear that cocaine exposure terminated at the first sign of impregnation leaves little adverse effect on the offspring. The

TABLE 4

THE DEVELOPMENTAL AND REPRODUCTIVE OUTCOME OF JUVENILE FEMALE MICE LISTED IN TABLE 3

Group	NO-sa00	SA-cc20	CC-cc00	CC-cc20	CC-cc40
Age in days for					
Showing plug	36.1 ± 0.2	36.1 ± 0.4	37.2 ± 0.4	37.0 ± 0.5	39.5 ± 0.6*†‡
Number (%) of animals					
Plugged	15 (100%)	15 (100%)	15 (93.8%)	15 (93.8%)	13 (81.2%)
Pregnant	14 (93.3%)	14 (93.3%)	14 (87.5%)	14 (87.5%)	11 (68.8%)
Lost pups in week 1	4 (28.6%)	0 (0%)*	4 (28.6%)	1 (7.1%)	3 (27.3%)
Gestation (days)	19.3 ± 0.2	18.9 ± 0.1*	18.9 ± 0.2*	19.0 ± 0.0	19.1 ± 0.1
Male ratio	0.48 ± 0.03	0.51 ± 0.04	0.49 ± 0.05	0.46 ± 0.04	0.42 ± 0.05
Litter size					
Day 1	10.7 ± 0.6	10.9 ± 0.3	10.7 ± 0.7	11.1 ± 0.6	10.4 ± 0.8
Day 7	9.7 ± 0.9	10.9 ± 0.3	10.4 ± 0.7	11.1 ± 0.6	9.8 ± 0.7
Averaged pup weight (g)					
Day 1	1.62 ± 0.04	1.60 ± 0.03	1.54 ± 0.03	1.59 ± 0.03	1.58 ± 0.02
Day 7	4.49 ± 0.23	4.31 ± 0.12	4.16 ± 0.21	4.20 ± 0.14	4.34 ± 0.14

Values listed are either counts or means ± SEM.
*Significantly different from NO-sa00 controls, $p < 0.05$.
†Significantly different from CC-cc00, ‡significantly different from CC-cc20; $p < 0.05$. Comparisons are made among the offspring of CC mothers only.

majority of young female mice receiving daily cocaine treatment were impregnated within the designated period. Prior cocaine exposure did not prolong their gestation period nor did it increase their chance to lose pups during the first postnatal week. In addition, no difference between treated and control mice was found in the sex ratio, the birth weight, or the postnatal weight gain of their pups. The cocaine-treated females in Experiment 1 gave birth to fewer pups than the saline-treated controls, but animals received high dose cocaine treatment in Experiment 2 gave birth to about the same number of pups as the untreated controls. The discrepancy might have been caused by a seasonal ceiling on litter size.

In a review, Smith and Asch (14) stated "Most neuroactive drugs produce only transient effects on the central nervous pathways necessary for normal gonadotropin secretion. The disruptive effects of these drugs are likely to be transient and completely reversible, and tolerance to the inhibitory drug effects may occur even with continued drug use." The results of our study agree with their hypothesis and support our previous finding that chronic cocaine exposure has only a limited effect on the reproduction in mice (2,3). Mice treated with a low dose of cocaine for extended periods apparently cope with the adverse effect of the chemical stimulant. Mice treated with a high dose of cocaine showed inhibited growth and development but, given enough time to reach puberty and a chance to mate, many of them were able to reproduce successfully.

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